

REVIEW

Year in review 2010: *Critical Care* – respirology

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Abstract

In this review, 21 original papers published last year in the respirology and critical care sections of *Critical Care* are classified and analyzed in the following categories: mechanical ventilation, lung recruitment maneuvers, and weaning; the role of positive end-expiratory pressure in acute lung injury models; animal models of ventilator-induced lung injury; diaphragmatic dysfunction; the role of mechanical ventilation in heart-lung interaction; and miscellanea.

Introduction

Treatment of acute respiratory failure is one of the most difficult challenges in intensive care unit (ICU) management. The most important advance in decreasing mortality in patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) has been the use of a low-tidal volume, lung protective ventilation strategy [1]. As such, there has been extensive research to explore the mechanisms of ALI in order to develop novel therapeutic approaches. Here, we review the key respiratory failure papers that appeared last year in *Critical Care*.

Mechanical ventilation, lung recruitment maneuvers, and weaning

Ventilation and perfusion mismatch, as a consequence of lung injury, leads to hypoxemia and can lead to hypercapnia. A previous study demonstrated that elevated values of dead-space fraction (V_d/V_t) are associated with increased risk of death in patients with ARDS [2].

Siddiki and colleagues [3] examined the utility of bedside calculation of pulmonary V_d/V_t in predicting the prognosis of patients with ALI/ARDS. The goal of the authors was to calculate V_d/V_t by using variables, such as minute ventilation (VE) and the arterial tension of carbon dioxide (P_aCO_2), that are readily available at the bedside. The

authors used the rearranged alveolar gas equation: $V_d/V_t = 1 - [(0.86 \times VCO_{2est})/VE \times PaCO_2]$, where VCO_{2est} represents the estimated carbon dioxide production derived from the modified Harris-Benedict equation. Data from two large databases of approximately 2,000 patients in total were used to calculate the V_d/V_t on days 1 and 3 of admission. A contingency analysis showed that higher V_d/V_t values were associated with higher mortality. For example, V_d/V_t values of less than 0.4 and greater than 0.8 were associated with hospital mortality rates of about 20% and 50%, respectively. This relationship was valid after adjustment for Acute Physiology and Chronic Health Evaluation III (APACHE III) score, presence of shock, hypoxemia, and positive end-expiratory pressure (PEEP).

De Robertis and colleagues [4] employed two techniques to decrease dead space: flushing the ventilator circuit and aspiration of dead space (ASPID). In healthy pigs ventilated at a respiratory rate of up to 60 breaths per minute, the authors demonstrated that circuit flushing and ASPID were able to reduce the $PaCO_2$ by 26% and 41%, respectively. These techniques are likely to be much more effective in healthy lungs than lungs with ALI, which have a high alveolar dead space. In addition, the combined effect of these two strategies to minimize dead space in ARDS remains to be determined.

In patients with otherwise-healthy lungs, the use of mechanical ventilation (MV) with large tidal volume, along with higher transpulmonary pressures, has been associated with the development of ALI/ARDS [5-7]. The predisposing factor for the development of ALI/ARDS is the duration of MV or an underlying systemic inflammatory response or both [8,9]. Two studies published in *Critical Care* expanded these findings, supporting the concept that low-tidal volume ventilation prevents the development of ALI and attenuates innate immune response activation [6,10].

Pinheiro de Oliveira and colleagues [10] randomly assigned 20 patients without ALI to low-tidal volume MV (5 to 7 mL of predicted body weight, or PBW) or high-tidal volume MV (10 to 12 mL/PBW). Patients in the lower tidal volume arm of the study had an attenuation of the lung inflammatory response after 12 hours, as demonstrated by reductions in bronchoalveolar lavage (BAL) concentrations of tumor necrosis factor-alpha (TNF- α) and interleukin-8 (IL-8).

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In a larger prospective randomized clinical trial, Determann and colleagues [6] demonstrated that patients who initially did not have ALI were less likely to develop ALI if they were ventilated with a low-tidal volume strategy. One hundred fifty patients without ALI were randomly assigned to receive a tidal volume of 6 or 10 mL of PBW. The group of patients treated with lower tidal volumes had lower IL-6 plasma levels compared with the group ventilated with conventional tidal volume. Underlying risk factors for the development of ALI, oxygenation index, number of transfused blood products, and the baseline lung lavage-fluid IL-6 level were all associated with lung injury in the univariate analysis. Moreover, a multivariate analysis showed that tidal volume, together with the level of PEEP, was an independent predictor of ALI/ARDS development. However, the study was not powered to investigate various risk factors for ALI/ARDS separately in a multivariate model; it is possible that the PEEP levels may be simply a marker of disease severity. Unfortunately, this study was stopped early at the second interim analysis, even though the trends for duration of MV and mortality rate in the two groups were similar. This early stopping may have overestimated the treatment effects [11].

Constantin and colleagues [12] showed the beneficial effect of lung recruitment maneuvers (LRMs) in reversing acute hypoxemia immediately after intubation for acute respiratory failure. In this study, 44 patients with acute respiratory failure were randomly assigned to receive 40 cm H₂O LRM for 30 seconds, or not, within 2 minutes after intubation. The patients treated with LRM had better oxygenation 5 minutes after intubation and this improvement persisted up to 30 minutes. The LRM strategy was not associated with significant hemodynamic impairment. After intubation, about 30% of the patients in both groups had blood cultures that were positive for the same bacteria that were present in the tracheal aspirate. However, as opposed to MV, LRM does not seem to be a risk factor for bacterial translocation.

Liberation from MV is one of the major challenges in the management of critically ill patients. Time spent in the weaning process represents 40% to 50% of the total duration of MV [13]. Many factors may negatively affect the ability to wean a patient from ventilator support. Neuropsychological problems play a significant role. Among these problems, agitation after withdrawal of sedation may have a great impact. Sztrymf and colleagues [14] showed the beneficial effect of loxapine, a neuroleptic agent, in mitigating agitation and facilitating weaning. Patients who were ventilated for more than 48 hours, who were ready for weaning, and who exhibited agitation after the reduction or withdrawal of sedation (a combination of benzodiazepines and opioid) were eligible for this study. Loxapine was well tolerated and significantly

reduced agitation, as assessed by three different agitation scales, and improved breathing patterns until 180 minutes after administration.

Tracheostomy is advised for patients undergoing prolonged ventilation to improve patient comfort, reduce sedation, and facilitate liberation from MV. In a retrospective observational study, Wu and colleagues [15] compared the outcome of patients ventilated via tracheostomy or via the translaryngeal route in a respiratory care center. In this specific population, weaning success was similar in the two groups; however, there was a trend to lower mortality in the tracheostomy group.

The role of positive end-expiratory pressure in acute lung injury models

Increased vascular permeability and lung edema are the key features of ALI and ARDS. PEEP is applied during MV to increase functional residual capacity (FRC), to redistribute edema fluid, and to decrease ventilator-induced lung injury (VILI). Alveolar fluid clearance (AFC) by alveolar epithelial cells is a major mechanism for edema resolution after injury. In healthy pigs, Garcia-Delgado and colleagues [16] showed that PEEP actively participates in AFC. The authors demonstrated that, after intra-tracheal administration of saline (4 or 10 mL/kg), PEEP of 10 cm H₂O induced an increase in AFC, which occurred earlier in the presence of less severe edema.

In recent years, the role of PEEP has been extensively investigated to clarify its physiological effects in patients with ARDS and to define its role in protective ventilation strategies. However, after exciting results of the ARMA (Respiratory Management in Acute Lung Injury/Acute Respiratory Distress Syndrome) study limiting tidal volume, three randomized controlled trials failed to demonstrate further improvement in mortality by higher PEEP levels [17]. Higher PEEP levels can increase the end-expiratory lung volume, but degree of recruitability is quite variable in patients with ARDS [18], and not all patients with ARDS may benefit from higher levels of PEEP. An ideal PEEP level in each patient should be set on the basis of individualized and physiologically based measurements.

Krebs and colleagues [19] demonstrated that an 'open lung' ventilation strategy using high-frequency oscillation ventilation (HFOV) or conventional mechanical ventilation (CMV) has the potential to mitigate VILI compared with CMV with low PEEP. After surfactant lavage, rats were randomly assigned to one of three ventilation strategies: CMV with low PEEP, CMV with high PEEP, or HFOV. The open lung approach, whether applied with CMV or HFOV, reduced VILI compared with the low-PEEP group. HFOV was superior to CMV only with respect to oxygenation. A notable strength of this study was the physiological method used to set PEEP in the

CMV open lung group; this PEEP value corresponded to the minimum respiratory system elastance. Moreover, to make the two ventilation strategies comparable, the investigators set the HFOV mean airway 2 cm H₂O above the mean airway pressure measured during CMV and 'best PEEP'.

Assisted modes of MV have the potential to maintain diaphragm activation, which can be associated with clearance of some atelectatic areas in the dependent lung zones. There are two potential advantages: first, improvement in gas exchange by a reduction of shunt and, second, attenuation of VILI by a reduction of non-aerated and overinflated area. Using a surfactant lavage model, Gama de Abreu and colleagues [20] randomly assigned pigs to one of three different ventilation strategies: pressure support ventilation (PSV), bilevel positive airway pressure (BPAP) + spontaneous breathing (SB), and BIPAP without SB. Compared with the PSV strategy, the BIPAP + SB strategy was able to reduce the amount of opening/closing and hyperinflated area as assessed by dynamic computed tomography (CT) scan analysis of the lung. Moreover, this aeration pattern was associated with a lower tidal volume. Interestingly, the SB activity during BIPAP may mitigate some mechanism of VILI, but further studies are warranted.

Electrical impedance tomography is a relatively new non-invasive, real-time, radiation-free, bedside imaging tool that has the potential to individualize lung protective ventilation. It is based on the principle that electrical currents generated at the surface of the thorax result in different voltages, depending on the underlying tissue impedance. A reconstruction algorithm gives the anatomical distribution of ventilation or perfusion of the area of interest or both. The global inhomogeneity (GI) index was recently introduced to quantify the degree of inhomogeneity of lung aeration and may be useful in minimizing the risk of volutrauma and atelectrauma. Zhao and colleagues [21] demonstrated, in 10 healthy anesthetized patients, that the PEEP value identified at the lowest value of the GI index was in good agreement with the PEEP value derived by the maximum global dynamic compliance and the compliance-volume curve methods. However, future studies to address the feasibility of this approach in patients with ALI/ARDS are needed.

Severe abdominal hypertension may be associated with a critical FRC reduction caused by a collapse of dependent lung areas and by increasing chest wall elastance. Regli and colleagues [22] demonstrated, in a pig model of abdominal hypertension, that predetermined PEEP levels of up to 15 cm H₂O were not able to counterbalance the FRC decrease induced by the high abdominal pressure of 26 mm Hg. This study highlighted the critical role of transpulmonary pressure as a key determinant of alveolar

recruitment and VILI, especially when chest wall elastance is increased.

MV with higher PEEP levels and LRMs may be part of a lung protective ventilation strategy [23]. Hypotension is one of the most common complications during the application of LRM. To counterbalance the negative effect of LRM on venous return, fluid boluses are used. In a sepsis model of ALI and 1 hour of MV, Silva and colleagues [24] shed light on the potential detrimental effects of hypervolemia by increasing shear stress injury to the lung. The authors demonstrated that hypervolemia (with colloid infusion) and LRM were associated with increased lung injury and higher inflammatory and fibrogenic responses as demonstrated by a more pronounced detachment of the alveolar-capillary membrane, increased levels of vascular cell adhesion molecule-1 (VCAM-1), and procollagen III (PC III) mRNA lung expression.

Animal models of ventilator-induced lung injury

MV with high pressures, in the absence of adequate levels of PEEP, has been shown to cause lung injury, including pulmonary edema, epithelial/endothelial cell damage, and innate immune responses such as neutrophil recruitment and macrophage activation. Statins have been shown to modulate the inflammatory immune response during ischemia-reperfusion [25], peritonitis [26], and aerosolized lipopolysaccharide (LPS) [27], likely by their inhibition of the hydroxy-methylglutaryl coenzyme A reductase. All of these conditions can induce lung injury and may be exacerbated by MV. Müller and colleagues [28] showed, in a mouse model of VILI, that the administration of simvastatin mitigated lung injury caused by large-tidal volume MV. Mice treated with simvastatin had greater oxygenation, better vascular integrity, and less pulmonary inflammation. Moreover, simvastatin treatment mitigated endothelial cell injury as demonstrated by a reduction in cell swelling as assessed by electron microscopy.

Neutrophilic alveolitis is a cardinal feature of the acute phase of ALI/ARDS. Modulation of the neutrophil inflammatory response could be important in improving outcomes in ALI/ARDS. Neutrin 1 is a protein, first described in central nervous system development, which is downregulated in the lung during the acute phase of ALI. Mutz and colleagues [29] showed that, after ALI was induced by LPS challenge, the anti-inflammatory protein neutrin 1, nebulized into the lungs of pigs or administered intravenously, attenuated the lung and systemic inflammatory response. The treated animals had decreased histopathological signs of pulmonary inflammation and a reduction of BAL and serum concentrations of IL-6 and TNF- α . Notably, the efficacy of the intervention was also evident on the degree of pulmonary edema and infiltrates on CT scan.

Mechanical stretch of the lung enhances oxidative stress [30,31], which can contribute to the pathogenesis of VILI by increasing alveolar and vascular permeability [32,33]. Recently, molecular hydrogen (H_2) was shown to selectively reduce the hydroxyl radical, which is the most cytotoxic of reactive oxygen species (ROS) [34]. In a mouse model of VILI, Huang and colleagues [35] compared the inhalation of two different gases: nitrogen and hydrogen. Compared with inhalation of nitrogen, that of hydrogen mitigated VILI. Inhalation of hydrogen was associated with increased expression of anti-apoptotic genes and with an attenuation of histopathological and inflammatory markers of VILI.

Diaphragmatic dysfunction: the role of mechanical ventilation and endotoxemia

Controlled MV is one of the most important risk factors for diaphragm dysfunction and is associated with rapid atrophy and enhanced muscular proteolysis [36]. Moreover, muscular weakness is an important disability in ARDS survivors [37].

In a small series of 10 ICU patients, Hermans and colleagues [38] measured twitch transdiaphragmatic pressure (TwPdi) by using bilateral anterior magnetic phrenic nerve stimulation (BAMPS). They demonstrated a 70% reduction in diaphragm force compared with healthy individuals; most of the patients were septic and had received corticosteroids. Moreover, there was a logarithmic relationship between TwPdi and the duration of MV and cumulative dose of piritramide and propofol.

ICU-acquired muscular weakness is a common complication of critical illness; moreover, its incidence in the subgroup of patients with sepsis has been reported to be 50% to 100%. Increased proteolysis by activation of the proteasome system, oxidative stress, and acquired channelopathy involving dysregulation of sodium channels have all been shown to participate in sepsis-induced muscular weakness. Labbe and colleagues [39] highlighted the importance of protein monocyte chemoattractant protein-1 (MCP-1) as contributing to diaphragm weakness after endotoxemia. In a mouse model of endotoxemia, there was impairment of diaphragmatic contractility along with upregulation of MCP-1. Treatment with an antibody blocking MCP-1 restored the force frequency of the diaphragm to levels observed in non-septic mice. Of note, the increased expression of MCP-1 after the endotoxic challenge was not associated with increased leukocyte infiltration, suggesting a direct role of the protein in the pathogenesis of endotoxic diaphragm weakness.

Effects of mechanical ventilation on heart-lung interactions

Non-invasive ventilation – continuous positive airway pressure (CPAP) and non-invasive BIPAP ventilation – are

considered safe and effective treatment options in acute cardiogenic pulmonary edema (ACPE) [40]. In a retrospective study, Aliberti and colleagues [41] demonstrated that the majority of patients with ACPE had acidosis on arrival to the emergency department. CPAP corrected the acidosis in many of these patients. Moreover, in patients treated with CPAP, the presence of both respiratory and metabolic acidosis was not a risk factor for clinical deterioration as determined by the need for BIPAP, tracheal intubation, and hospital mortality.

Right ventricle (RV) dysfunction and failure are serious conditions in the ICU, usually occurring in the context of left ventricular failure, pulmonary embolism, pulmonary hypertension, sepsis, or ALI or after cardiothoracic surgery. RV dysfunction is difficult to diagnose and manage at the bedside. In a systematic review of the literature, Price and colleagues [42] provided an excellent overview of the pathogenesis, diagnosis, and treatment options, focusing on the most commonly used vasoactive drugs to improve RV function and to reduce afterload. Of interest, Guyatt and colleagues [43] used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system to make recommendations that potentially could help clinicians face this challenging heart dysfunction.

Miscellanea

Ischemia reperfusion injury, as occurs in the post-resuscitative phase of hemorrhagic shock, is characterized by organ damage caused by activation of the innate immune response and oxidative stress. Ganster and colleagues [44] used a rat model of ischemia reperfusion injury induced by controlled hemorrhage and demonstrated that sodium hydrosulfide treatment significantly reduced vascular dysfunction *in vivo* and release of ROS *in vitro* as demonstrated by paramagnetic resonance in the heart and aorta.

Abbreviations

ACPE, acute cardiogenic pulmonary edema; AFC, alveolar fluid clearance; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ASPID, aspiration of dead space; BAL, bronchoalveolar lavage; BIPAP, bilevel positive airway pressure; CMV, conventional mechanical ventilation; CPAP, continuous positive airway pressure; CT, computed tomography; FRC, functional residual capacity; GI, global inhomogeneity; HFOV, high-frequency oscillation ventilation; ICU, intensive care unit; IL, interleukin; LPS, lipopolysaccharide; LRM, lung recruitment maneuver; MCP-1, monocyte chemoattractant protein-1; MV, mechanical ventilation; $PaCO_2$, arterial tension of carbon dioxide; PBW, predicted body weight; PEEP, positive end-expiratory pressure; PSV, pressure support ventilation; ROS, reactive oxygen species; RV, right ventricle; SB, spontaneous breathing; TNF- α , tumor necrosis factor-alpha; TwPdi, twitch transdiaphragmatic pressure; VCO_{2est} , estimated carbon dioxide production; Vd/Vt , dead-space fraction; VE, minute ventilation; VILI, ventilator-induced lung injury.

Competing interests

The authors declare that they have no competing interests.

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